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Attorney's Docket No.: 10274-034001 / A061

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mundy et al.
Serial No. : 09/805,840
Filed : March 13, 2001
Title : METHODS OF TREATING MULTIPLE MYELOMA AND MYELOMA-INDUCED BONE RESORPTION USING INTEGRIN ANTAGONISTS

Art Unit : 1644
Examiner : Maher M. Haddad, Ph.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GREGORY MUNDY AND TOSHIYUKI YONEDA UNDER 37 C.F.R. §1.131

We, Gregory Mundy, a citizen of U.S.A. residing at 3719 Morgan's Creek, San Antonio, Texas, and Toshiyuki Yoneda, a citizen of Japan residing at 3530 Hunters Sound, San Antonio, Texas, hereby declare as follows:

1. We are the co-inventors of the subject matter disclosed and claimed in the above-referenced U.S. patent application.

2. We are familiar with the present claims of the application, which are directed to methods of treating multiple myeloma. The methods include administering to an individual a therapeutically effective amount of a composition comprising an anti-alpha4 integrin antibody homolog or antigen binding fragment thereof.

3. The present application claims priority to U.S. Provisional Application 60/100,182 filed September 14, 1998.

4. Van Zaanen et al. (1998; *Br. J. Haematol.*102:783-90) was published August 18, 1998, as shown by the date stamped copy of the reference enclosed herewith. Van Zaanen et al. disclose chimeric anti-IL6 monoclonal antibodies in the treatment of multiple myeloma.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

January 30, 2004
Date of Deposit

Bernadette Fallon
Signature

BERNADETTE FALLON
Typed or Printed Name of Person Signing Certificate

5. We conceived and reduced to practice the claimed invention prior to the publication date of Van Zaanen et al..

6. We submit herewith, as Exhibit A, a copy of a document presented at a laboratory meeting that took place prior to the publication date of Van Zaanen et al. in the laboratory of Toshiyuki Yoneda. As discussed in detail below, Exhibit A shows evidence of actual reduction to practice of the claimed invention prior to the effective publication date of Van Zaanen et al. The specific date of creation of Exhibit A has been redacted.

7. Exhibit A describes and summarizes the results of *in vivo* data showing that in mice injected with 5TGM1 multiple myeloma cells, treatment with anti-VLA-4 antibody decreased the levels of IgG2b (the antibody isotype produced by 5TGM1 myeloma cells) and the incidence of paraplegia, a symptom of multiple myeloma. Exhibit A thus shows that the idea of treating multiple myeloma in a subject with an anti-VLA-4 antibody was conceived and actually reduced to practice before the publication date of Van Zaanen et al.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1-23-04
Date

Gregory Mundy

Date

Toshiyuki Yoneda

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225 Franklin Street
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_____
Date

Gregory Mundy

1/26/04
Date

Toshiyuki Yoneda

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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Exhibit A

Background

Almost all myeloma patients demonstrate α4 integrin expression.

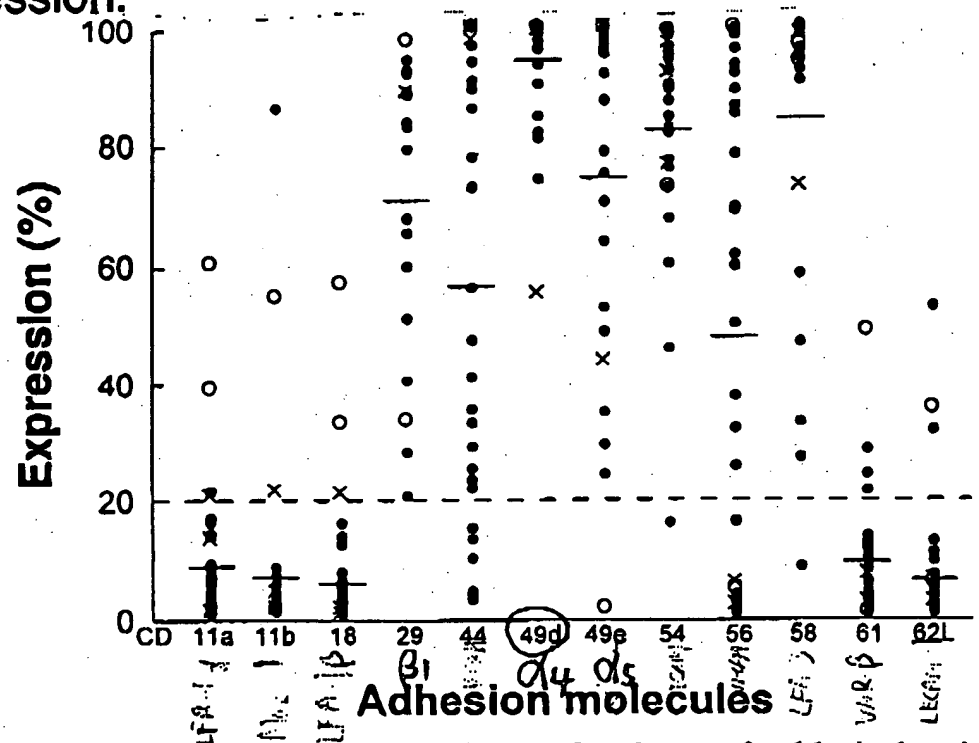


Fig. 2. Expression of adhesion molecules on freshly isolated CD38⁻ myeloma cells. The fresh myeloma cells were obtained from 26 patients with multiple myeloma (●), 2 with aggressive myeloma (○), and 3 with PCL (×). Horizontal lines represent the mean percentage expression of adhesion molecules. (Tatsumi et al: Jpn J Cancer Res 1996)

Anti-α4β1 Ab blocks the attachment of 5TGM1 cells to ST2 and osteoclastogenesis in vitro. (Michigami)

Approach

Treat 5TGM1-bearing mice with anti-α4 integrin (PS/2)

Protocol

Exp.1 C57BL/KaLwRij mice

I PBS

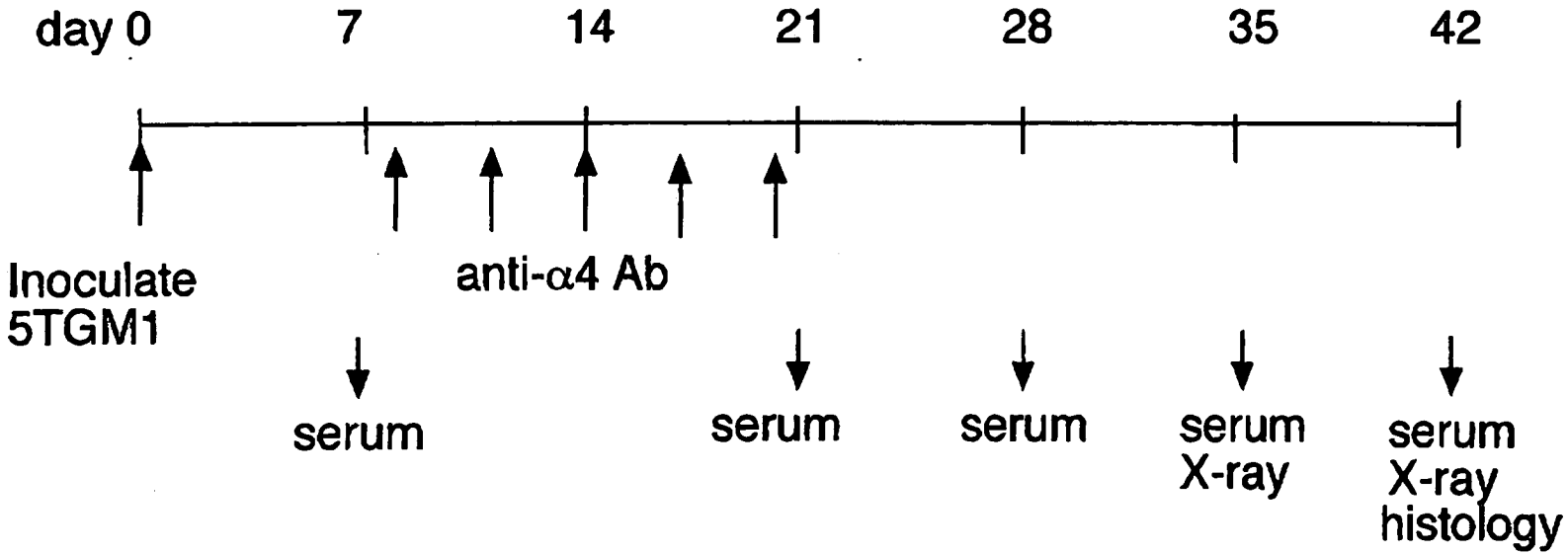
II anti-α4 40 μg

III anti-α4 80 μg

Exp.2 Nu/Bg/XID mice

I PBS

II anti-α4 80 μg



Result at 5 weeks

Exp.1 C57BL/KaLwRij mice

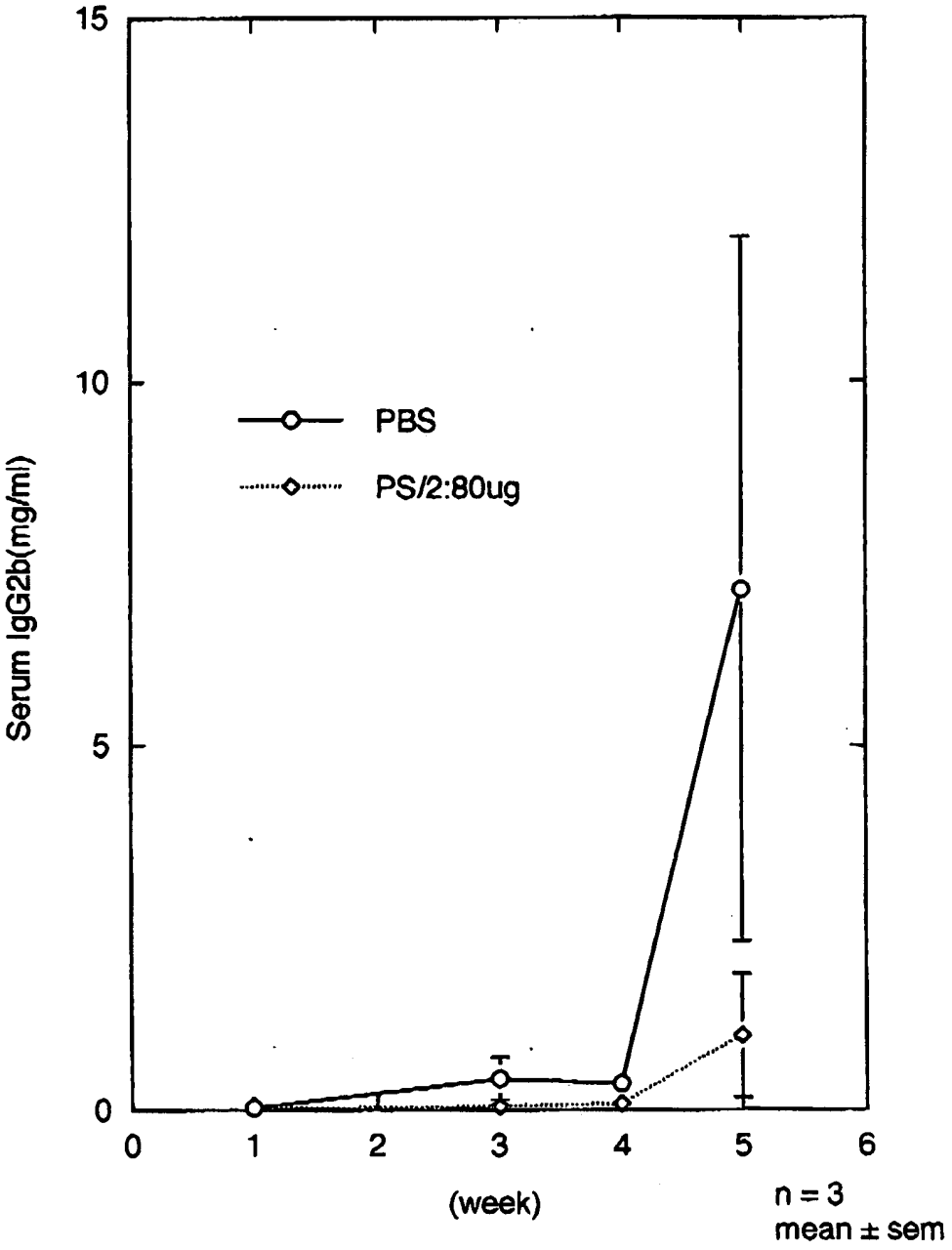
No hypercalcemia and paraplegia.

Ab-treated mice shows smaller increase of serum IgG2b than untreated mice.

Exp.2 Nu/Bg/XID mice

group	PBS			anti-α4		
mouse	a	b	c	a	b	c
paraplegia	+	-	-	-	-	-
Ca2+ (mM)	1.14	1.26	1.29	1.21	1.25	1.28
IgG2b (mg/ml)	0.40	16.54	4.51	0.27	0.06	2.70

Anti-α4 Ab Blocks IgG2b Elevation of 5TGM1-Bearing Nu/Bg/XID Mice



Conclusion

Blocking α4 integrin is a potential therapeutic approach.

Questions

Mechanism by which anti-α4 decreases IgG2b

Effects on osteolytic lesions

→X-ray, histology